Amendments to the Specification:

Please replace the paragraph beginning at page 6, line 15, with the following paragraph.

In another aspect, the invention features ~~a~~ an IAP or NAIP ~~gene nucleic acid fragment or~~ antisense ~~RNA sequence~~ oligonucleotide for use in suppressing cell proliferation. Such nucleic acids of the invention and methods for using them may be identified according to a method involving: (a) providing a cell sample; (b) introducing by transformation into the cell sample a candidate IAP or NAIP ~~nucleic acid~~ antisense oligonucleotide; (c) expressing the candidate IAP or NAIP ~~nucleic acid~~ antisense oligonucleotide within the cell sample; and (d) determining whether the cell sample exhibits an altered apoptotic response, whereby ~~decreased~~ increased apoptosis identifies an anti-proliferative compound. Preferably, the cell is a cancer cell.

Please replace the paragraph beginning at page 8, line 23, with the following paragraphs.

In another aspect, the invention features a method of treating a patient diagnosed with a proliferative disease. In the method, apoptosis may be induced in a cell to control a proliferative disease either alone or in combination with other therapies by administering to the cell a negative regulator of the IAP-dependent or NAIP anti-apoptotic pathway. The negative regulator may be, but is not limited to, an IAP ring zinc finger, and an IAP polypeptide that includes a ring zinc finger and lacks at least one BIR domain. Alternatively, apoptosis may be induced in the cell by administering a nucleic acid encoding an IAP antisense ~~RNA molecule~~ oligonucleotide administered directly or via gene therapy (see U.S. Pat. No. 5,576,208 for general parameters which may be applicable in the selection of IAP or NAIP antisense ~~RNAs~~ oligonucleotides).

[T]he term "oligonucleotide" refers to an oligomer or polymer of ribonucleic acid or deoxyribonucleic acid. This term includes oligomers consisting of naturally occurring bases, sugars and intersugar (backbone) linkages as well as oligomers having non-naturally occurring portions which function similarly. Such modified or substituted oligonucleotides are often preferred over native forms because of properties such as, for example, enhanced cellular uptake and increased stability in the presence of nucleases.

Specific examples of some preferred oligonucleotides envisioned for this invention may contain phosphorothioates, phosphotriesters, methyl phosphonates, short chain alkyl or cycloalkyl intersugar linkages or short chain heteroatomic or heterocyclic intersugar linkages. Most preferred are those with CH_2 --NH--O--CH_2, CH_2 --N(CH_3)--O--CH_2, CH_2 --O--N(CH_3)--CH_2, CH_2 --N(CH_3)--N(CH_3)--CH_2 and O--N(CH_3)--CH_2 --CH_2 backbones (where phosphodiester is O--P--O--CH_2). Also preferred are oligonucleotides having morpholino backbone structures. Summerton, J.E. and Weller, D.D., U.S. Pat. No: 5,034,506. In other preferred embodiments, such as the protein-nucleic acid (PNA) backbone, the phosphodiester backbone of the oligonucleotide may be replaced with a polyamide backbone, the bases being bound directly or indirectly to the aza nitrogen atoms of the polyamide backbone. P.E. Nielsen, M. Egholm, R.H. Berg, O Buchardt, Science 199, 254, 1497. Other preferred oligonucleotides may contain alkyl and halogen-substituted sugar moieties comprising one of the following at the 2' position: OH, SH, SCH_3, F, OCN, $O(CH_2)_n$ NH_2 or $O(CH_2)_n$ CH_3 where n is from 1 to about 10; C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl or aralkyl; Cl; Br; CN; CF_3 ; OCF_3 ; O--, S--, or N-alkyl; O--, S--, or N-alkenyl; $SOCH_3$; SO_2 CH_3 ; ONO_2 ; NO_2 ; N_3 ; NH_2 ; heterocycloalkyl; heterocycloalkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a conjugate; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide; or a group for improving the pharmacodynamic properties of an oligonucleotide and other substituents having similar properties. Oligonucleotides may also have sugar mimetics such as cyclobutyls in place of the pentofuranosyl group.

Other preferred embodiments may include at least one modified base form. Some specific examples of such modified bases include 2-(amino)adenine, 2-(methylamino)adenine, 2-(imidazolylalkyl)adenine, 2-(aminoalklyamino)adenine or other heterosubstituted alkyladenines. In yet another method, the negative regulator may be a purified antibody, or a fragment thereof, that binds specifically to an IAP polypeptide. For example, in one preferred embodiment, the antibody may bind to an approximately 26 kDa cleavage product of an IAP polypeptide that includes at least one BIR domain but lacks a ring zinc finger domain.

Please replace the paragraph beginning at page 9, line 13, with the following paragraph.

In two additional aspects, the invention features a transgenic animal and methods of using the mammal for detection of anti-cancer therapeutics. Preferably the mammal overexpresses an IAP or NAIP polypeptide and/or expresses a NAIP

or IAP antisense ~~RNA~~ oligonucleotide or IAP or NAIP fragment. In one embodiment, the animal also has a genetic predisposition to cancer or has cancer cells under conditions which provide for proliferation absent the transgenic construct encoding either the antisense ~~RNA~~ oligonucleotide or fragment.

Please replace the paragraph beginning at page 16, line 10, with the following paragraph.

By "antisense," as used herein ~~in reference to nucleic acids,~~ is meant ~~a nucleic acid sequence~~ an oligonucleotide, regardless of length, that is complementary to the coding strand of an IAP or NAIP gene. Preferably, the antisense ~~nucleic acid~~ oligonucleotide is capable of enhancing apoptosis when present in a cell which normally does not undergo sufficient apoptosis. Preferably, the increase is at least 10%, relative to a control, more preferably 25%, and most preferably 1-fold or more.

Please replace the paragraph beginning at page 17, line 15, with the following paragraph.

Fig. 5 is the murine hiap-1 (also referred to as "miap-1") cDNA sequence (SEQ ID NO:~~39~~11) and the encoded murine HIAP-1 polypeptide sequence (SEQ ID NO:~~40~~12).

Please replace the paragraph beginning at page 17, line 18, with the following paragraph.

Fig. 6 is the murine hiap-2 (also referred to as "miap-2") cDNA sequence (SEQ ID NO:~~41~~13) and the encoded murine HIAP-2 polypeptide (SEQ ID NO:~~42~~14).

Please replace the paragraph beginning at page 25, line 5, with the following paragraph.

We have documented that overexpression of the IAPs renders cell lines resistant to serum growth factor withdrawal, tumor necrosis factor alpha (TNF) and menadione exposure, all of which are treatments that normally induce apoptosis. Herein we describe the extension of these studies to cancer cell lines using apoptotic triggers used in clinical situations, such as doxorubicin, adriamycin, and methotrexate. Our findings have led up to design antisense ~~RNA~~ oligonucleotide therapeutics. Rapid screening of multiple cell lines for apoptotic response has been made feasible through the generation of a series of sense and antisense adenoviral IAP and NAIP expression vectors, as well as control lacZ viruses. One may now show enhanced drug resistance using the expression constructs. In addition, anti-sense adenovirus constructs may be developed and used to test reversal of the drug resistant phenotype of appropriate cell lines. We have surveyed cancer cell lines with the objective of identifying tumor types in which IAP overexpression is apparent or altered and these results are described both above and in the Examples below. Concomitant to this research, we have designed a series of antisense oligonucleotides to various regions of each of the *iaps*. These ~~oligos~~ oligonucleotides may be used to enhance drug sensitivity after testing in an assay system, i.e., with the adenoviral vectors system. Animal modeling of the effectiveness of antisense IAP oligos may also be employed as a step in testing and appropriate transgenic mammals for this are described above and also generally available in the art.

Please replace the paragraph beginning at page 28, line 19, with the following paragraph.

An IAP mutant protein or protein fragment, a gene encoding the same, a gene encoding an IAP antisense ~~RNA~~ oligonucleotide, or modulator of an IAPs may be administered within a pharmaceutically-acceptable diluent, carrier, or excipient, in unit dosage form. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer the compounds to patients suffering from a disease that is caused by excessive cell proliferation. Administration may begin before the patient is symptomatic. Any appropriate route of administration may be employed, for example, administration may be parenteral, intravenous, intraarterial, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, suppository, or oral administration. For example, therapeutic formulations may be in the form of liquid solutions or suspensions; for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

Please replace the paragraph beginning at page 53, line 3, with the following paragraph.

2. Confirmation of recombinant adenovirus function. Verification of the sense adenovirus function involves infection of tissue culture cells and determination of protein expression levels. We have performed western blot analysis of several of the recombinant adenoviruses, including NAIP, XIAP and XIAP-ΔZF. The remaining viruses may be ready readily assessed for protein expression using the polyclonal IAP antibodies. Functional analysis of the antisense viruses may be done at the RNA level using either northern blots of total RNA harvested from infected tissue culture cells or ribonuclease protection assays. Western blot analysis of infected cells will be used to determine whether the expressed antisense ~~RNA~~ oligonucleotide interferes with IAP expression in the host cell.

Please replace the paragraph beginning at page 58, line 20, with the following paragraph.

Characterization of IAP genes provided information that necessary for generation IAP transgenic animal models to be developed by homologous recombination (for knockouts) or transfection (for expression of IAP fragments, antisense IAP ~~RNA~~ oligonucleotides, or increased expression of wild-type or mutant IAPs). Such models may be mammalian animal, e.g., a mouse. Such models are useful for the identification of cancer therapeutics alone or in combination with cancer inducing cells or agents, or when such mice are crossed with mice genetically predisposed to cancers.

Please replace the paragraph beginning at page 67, line 5, with the following paragraph.

In other embodiments, the invention includes use of any protein which is substantially identical to a mammalian IAP polypeptides (Figs. 1-6; SEQ ID NOs:1-~~42~~14); such homologs include other substantially pure naturally-occurring mammalian IAP proteins as well as allelic variants; natural mutants; induced mutants; DNA sequences which encode proteins and also hybridize to the IAP

DNA sequences of Figs. 1-6 (SEQ ID NOS:1-~~42~~14) under high stringency conditions or, less preferably, under low stringency conditions (e.g., washing at 2X SSC at 40°C with a probe length of at least 40 nucleotides); and proteins specifically bound by antisera directed to a IAP polypeptide. The term also includes chimeric polypeptides that include a IAP portion.